ORIGINAL ARTICLE

Implications of Serum Pepsinogen I in Early Endoscopic Diagnosis of Gastric Cancer and Dysplasia

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Background and Aims: The risk of gastric cancer (GCA) is increased in atrophic gastritis. A low serum pepsinogen group I (SPGI) level is a good serologic indicator of atrophic gastritis of the gastric corpus and fundus, and can be used for diagnosis of subjects with atrophic gastritis and of increased risk for GCA. The present study was undertaken to investigate whether SPGI assay and a diagnostic gastroscopy could enable the diagnosis of GCA at an early stage. **Material and Methods:** The study was carried out as part of the Alpha-Tocopherol, Beta-Carotene Cancer prevention study (ATBC study) in Finland, in which 22,436 male smokers aged 50–69 years were screened by SPGI. Low SPGI levels (< 25 μg/l) were found in 2196 (9.8%) men. Upper GI endoscopy (gastroscopy) was performed in 1344 men (61%) and 78% of these had moderate or severe atrophic corpus gastritis in endoscopic biopsies. A control series of 136 men from the ATBC study cohort with abdominal symptoms, but with SPGI ≥ 50 μg/l were similarly endoscopied, and 2.2% of these had corpus atrophy. **Results:** Neoplastic alterations were found in 63 (4.7%; 95% CI: 3.6%–5.8%) of the 1344 endoscopied men with low SPGI levels. Of these, 42 were definite dysplasias of low grade, 7 dysplasias of high grade, 11 invasive carcinomas, of which 7 were 'early' cancers, and 3 carcinoid tumors. In the control series, 1 man (0.7%) of the 136 men had a definite low-grade dysplasia. Thus, 18 (1.3%; 95% CI 0.7%–2.0%) cases with 'severe' neoplastic lesions (4 advanced cancers, 7 early cancers and 7 dysplasias of high grade) were found in the low SPGI group, but there were none in the control group. All four patients with advanced cancer died from the malignancy within 5 years (mean survival time 2.5 years), whereas surgical treatment in all those with early cancer or high-grade dysplasia was curative. One of the seven patients with early cancer and two of the seven with high-grade dysplasia died within 5 years, but none died from the gastric cancer. Thus, curative treatment was given to 14 of 18 men in whom a malignant lesion was found in gastroscopy. This is about 15% of all gastric cancer cases (92 cases) which were diagnosed within 5 years after SPGI screening in the 22,436 men. Among the gastric cancer cases of the main ATBC study, the 5-year survival rate was 33% (85% of the non-survivors died from gastric cancer). **Conclusions:** We conclude that assay of SPGI followed by endoscopy is an approach which can enable the early diagnosis of gastric cancer at a curable stage.

Key words: Atrophic gastritis; cancer prevention; dysplasia; gastric cancer; pepsinogen

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World-wide incidence of gastric cancer has declined markedly over the last few decades (1), but gastric cancer is still one of the most common malignancies in many countries. In addition to preventive measures, early diagnosis is a possible means of improving the prognosis of gastric cancer. This form of cancer is usually diagnosed at an advanced, late stage, and hence has a poor prognosis. Atrophic gastritis is a condition which clearly increases the risk of gastric cancer (2, 3). A low serum pepsinogen I (SPGI) level is a good serologic indicator of atrophic gastritis affecting the corpus and fundus of the stomach, and consequently it is conceivable that subjects with an increased risk of gastric cancer could be identified by screening the general population with a SPGI test (4).

Our present study was undertaken to investigate how well gastric cancers and precancer lesions (dysplasias) could be found using the SPGI test followed by endoscopy and biopsy in a free-living male population in a Western country, and whether this approach will improve the detection of gastric cancer at an early, curable stage, and thus improves its prognosis.

Materials and Methods

This study was done within the Alpha-Tocopherol, Beta-Carotene cancer prevention (ATBC) study, which was a randomized, double-blind, placebo-controlled trial to examine the effect of alpha-tocopherol and beta-carotene on the incidence of lung and other cancers (5, 6). The study was carried out in Finland in 1985–1993.

The rationale, design and methods of the ATBC study, and characteristics of the participants, have been described in detail elsewhere (5–7). The participants (n = 29,133) were recruited from the total male population aged 50 to 69 years living in southwestern Finland (n = 290,406). To be eligible, they had to be smokers (5 or more cigarettes per day at entry) and willing to give informed written consent.

Identifying subjects with atrophic gastritis

At baseline and after 3 years' intervention a blood sample was drawn from the study participants and serum stored at −70 °C. Serum pepsinogen I (SPGI) was determined from these samples in 22,436 subjects, still active participants in the ATBC study after a mean intervention of 4.8 years (7). Of these, 2196 men had SPGI <25 μg/l at either baseline or the 3-year sample. Of these, 852 (39%) men refused or did not respond, or were ineligible for gastroscopy for various health reasons, so that gastroscopy was finally done in 1344 (61%) men. Of these, 164 (12%) had resected stomachs, and, in these cases, biopsy specimens were available only from the corpus. All men with low SPGI levels were invited to gastroscopy whether or not they had dyspeptic symptoms.

Control series

Gastroscopy was also performed on 136 ATBC study participants who complained of dyspeptic symptoms, but had normal SPGI levels (≥50 μg/l) ('control series'). For ethical reasons, recruitment of this 'control series' with normal SPGI was limited only to men with marked dyspeptic symptoms.

Serum pepsinogen group I (SPGI) assay

Serum PGI analyses were done in two phases. First, SPGI levels were determined from serum samples of 6297 men in the laboratory of I. M. Samloff, Sepulveda, Calif., USA (8). The remaining serum samples from 16,049 men were analysed in the laboratory of M. Härkönen, Helsinki, Finland. The analyses were done by radioimmunoassay methods (9). The PGI used in the assay was purified by us in co-operation with Orion Diagnostica, Helsinki, Finland, and the method was calibrated against Dr. Samloff's reference standard. The antibody was raised in rabbits. PGI was iodinated with lactoperoxidase sorbent. After iodination, PGI was purified in a column (1 × 30 × m) with Sephadex G75 superfine. After every iodination the working dilution of the label was estimated to give 35,000 cpm and the antibody was diluted to give 30%–35% of total binding, being a 1:15,000 dilution of the stock solution (1:100 of whole antiserum).

Samples were prediluted 1:10 (final dilution 1:40) with a Hamilton diluter. Reference standards, prediluted samples and controls as well as diluted label and diluted antibody solution were placed in a TECAN RSP 5052 robots sample processor and pipetted using the following volumes: 100 μl of analytes, 200 μl of label, and 100 μl of antibody.

The tubes were incubated for 18 h overnight at 10 °C. Thereafter 1 ml of Decanting Solution 3 from Pharmacia, Sweden, was added and the tubes were further incubated for 1 h. After 10 min centrifugation at 1500 × the supernatants were decanted and the precipitates counted in a Wizard gamma counter (Wallac, Turku, Finland). The Wizard gamma counter was calibrated with ^{125}I and ^{129}I. The PGI results were calculated using the Wallac MultiCalc Program for radioimmunoassay with a smoothed spline function.

The serum dilution curve was parallel with the standard curve in the range of 1–100 μg/l using 0.04 mol/l phosphate buffered saline, pH 7.5, containing 1% bovine serum albumin. In every series, two control sera were included, at intervals of 100, and the quality control charts were plotted. Every 50th sample was assayed in duplicate. The interassay coefficients of variation calculated from control sera were between 10% and 13% (at the level between 3 and 50 μg/l).

To enable comparison of the two PGI methods (the Samloff method and the present one), 300 serum samples were measured with both methods. The best correlation was achieved by a second-degree polynomial model. The results of the present method were transformed to be compatible with the Samloff method.

The cut-off value for diagnosis of atrophic gastritis with the present method was determined by measuring 200 serum samples (serum PGI concentration 15–35 μg/l by Samloff method) by both methods.

Gastroscopy

Subjects with low SPGI levels were informed by letter about the biologic meaning of a low SPGI level, the risk of neoplastic lesions in atrophic gastritis, and the purpose of the present study. The letter contained an invitation to undergo endoscopy. After an inquiry into their health history respondents signed a written informed consent form and an outpatient endoscopy was performed.

Gastroscopy was performed with Olympus endoscopes in the standard manner. Routine biopsies were taken under visual control as follows: one from the distal and one from the proximal antrum along the lesser curvature, and two biopsies from the middle corpus, one from the anterior and one from the posterior wall. In addition, multiple biopsies were taken from all endoscopically abnormal lesions (local colour changes, ulcers, scars, abnormal folds, polypoid lesions, tumours).

The location of each biopsy was recorded. Specimens were fixed overnight in neutral buffered formalin, and then embedded in paraffin. Histologic sections were stained with hematoxylin-eosin, Alcian blue (PAS 2.5), and modified Giemsa methods.

Histology and diagnosis of malignancy and dysplasia

Gastritis was classified in all biopsies according to the guidelines of the Sydney System (10). Dysplasia was diagnosed when epithelial atypia (cellular atypia) occurred in association with abnormalities in differentiation of the epithelium, and with abnormalities in architecture of the gastric foveolae and glands, but without evidence of invasion (11–15).

Dysplasia was initially graded into three categories: mild, moderate, or severe (12). The mild category included cases in which the lesions were at most mild in degree, obscure, or indefinite. For instance, all cases with atypical immature metaplasia (intestinal metaplasia type II or III) without other dysplastic features were classified into this category. Moderate and severe categories included cases in which definite dysplasia could be established, e.g., all lesions with adenoma-like growth patterns without evidence of malignancy (invasion). Cases of 'carcinoma in situ'-type appearance (suspicion of malignancy without evidence of invasion) were classified as severe dysplasia. Carcinomas (tumours with definite invasion) and carcinoid tumours were noted separately.

Gastric carcinomas and carcinoid tumours, and dysplasias of moderate or severe grade, were considered to represent definite malignant or premalignant end-stage lesions. Cases were accepted as definite dysplasia only when independent evaluations of the lesions by two pathologists (Pentti Sipponen, Helsinki, and Klaus Lewin, Los Angeles) agreed. In three cases the opinions diverged, and these cases were classified as an indefinite category of dysplasia, considered non-dysplastic, and excluded from the endpoint analysis. Within the definite dysplasia category, the cases were further classified into 'definite dysplasia: low grade', and 'definite dysplasia: high grade', after discussion and mutual agreement between the two pathologists.

Table I. Gastric mucosal neoplasia in 1344 Finnish 50–69-year-old male smokers with low serum pepsinogen I (SPGI) levels

Type of neoplasia	*n*	%
Dysplasia	49	78
Low grade	42	67
High grade	7	11
Carcinoma	11	17
Early stage	7	11
Advanced stage	4	6
Carcinoid tumour	3	5
Total	63	100

Safety aspects

The gastritis substudy was accepted by the Ethical Issues' Committee of the National Public Health Institute, Helsinki, Finland. A Data and Safety Monitoring Committee convened twice annually throughout the study to review its progress and integrity, and to evaluate data relevant to safety.

Results

Identification of atrophic gastritis with SPGI

Upper GI endoscopy was performed in 1344 (61%) men with low SPGI levels, and of these, 1044 (78%) had either moderate or severe (advanced) atrophic gastritis of the corpus mucosa in endoscopic biopsies. The corpus mucosa was non-atrophic in 122 (9%) cases and showed mild atrophic gastritis in 178 (13%) cases. Correspondingly, 3 (2.2%) of 136 men with gastric symptoms and normal SPGI ('control series'; SPGI $\geq$ 50 μg/l) had moderate atrophic corpus gastritis (none had severe atrophic gastritis), and 14 (10%) men had mild atrophic gastritis. Thus, the likelihood of advanced (moderate or severe) atrophic gastritis in the population was 78% (95% CI: 75%–80%) when the SPGI level was $<$25 μg/l. Correspondingly, the likelihood of non-atrophic corpus mucosa was 98% (95%–100%) in the presence of SPGI levels $\geq$50 μg/l.

Gastric neoplasias in men with low SPGI levels

In all, 63 (4.7%; 95% CI: 3.6%–5.8%) of the 1344 gastroscopied men with low SPGI levels had either gastric carcinoma, carcinoid tumour, or definite dysplasia of high or low grade (Table I). In the control series with normal SPGI levels, only 1 (0.7%) of the 136 men had a dysplastic lesion of low grade. The sites of the neoplasias are presented in Table II, and the distribution of the lesions into different subcategories among the non-operated and operated patients (earlier partial gastrectomy for peptic ulcer disease) is presented in Table III.

There were 18 (1.3%; 95% CI: 0.7%–2.0%) men in whom the neoplastic lesion was considered to be 'severe' or 'advanced': 11 men with invasive cancer and 7 men with dysplasia of high grade. Seven (64%) of the 11 gastric

Table II. Site of the gastric mucosal neoplasia in 1344 50–69-year-old Finnish male smokers with low and normal serum pepsinogen I (SPGI) levels

	Site of the neoplastic lesion, n (% of total)					
SPGI level	Cardia	Corpus and fundus	Angulus	Distal stomach, antrum or pylorus	Anastomosis operated stomach	Total
Low SPGI (<25 μg/l)	2 (3%)	13 (21%)	19 (30%)	17 (27%)	12 (19%)	63 (100%)
Normal SPGI (≥50 μg/l)	0	0	0	1 (100%)	0	1 (100%)

carcinomas were 'early' carcinomas (invasion limited to submucosa at most) according to the final postoperative staging of the tumour. According to the Laurén classification, five of the carcinomas were of intestinal type and six were of non-intestinal (diffuse or unclassified) type.

Among 51 men with neoplasia of any type in an unoperated stomach (Table III), 45 (88%) had advanced (moderate or severe) atrophic gastritis in the corpus. The neoplastic lesion was located in the proximal part of the stomach (at the angulus or above) in 34 (67%), and in the distal stomach (antrum or pylorus) in 17 (33%) cases.

SPGI preceding clinical gastric cancer

In the entire ATBC study cohort, gastric cancer was diagnosed in 51 participants within 3 years since baseline; SPGI of the baseline serum samples was determined in 43 cases, and of these, 11 cases (26%) had SPGI levels <25 μg/l. Correspondingly, gastric cancer was diagnosed in 69 participants during the 4th to 7th years after the baseline, and low SPGI levels (<25 μg/l) were found in only 7 (10%) of these cases.

Follow-up and survival

All 11 gastric cancers detected by gastroscopy underwent surgery, which confirmed that 7 cancers were 'early' (invasion limited to submucosa at most) and 4 were advanced. None of the 4 patients with advanced cancer survived 5 years (mean survival time 2.5 years), whereas 6 of the 7 patients with 'early' cancer survived 5 years. One died of small cell lung cancer 3.6 years after gastroscopy without evidence of gastric cancer. Concerning the survival of the dysplasia cases found in gastroscopy, 2 of the 7 cases with high-grade dysplasia and 7 of the 42 cases with low-grade dysplasia died within 5 years of gastroscopy, but none died due to gastric cancer. For comparison, 121 gastric cancer cases (clinically diagnosed cancers other than those found by the present SPGI screening and endoscopy, or cancers that appeared before the SPGI screening and endoscopy) were diagnosed among the ATBC study participants during the intervention (median 6.1 years). Of these, only 33% survived 5 years and gastric cancer was the underlying cause of death in 85% of the deceased.

Altogether, 85 cases of gastric cancer, including the 11 cases found by gastroscopy in this study, were diagnosed within 5 years after the SPGI screening among the ATBC study participants. Assuming that the cases of early gastric cancer ($n = 7$) and those with high-grade dysplasia ($n = 7$) found in gastroscopy would have progressed to advanced gastric cancer in 5 years, it can be estimated that 14 of 92 (15%) cases were prevented from developing into clinical cancer by the SPGI screening and subsequent gastroscopy. Correspondingly, it may be assumed that 14 gastric cancer deaths were prevented.

Discussion

In the present study in male smokers of 50–69 years of age, advanced (moderate or severe) atrophic corpus gastritis was found in endoscopic biopsy specimens in 78% of those with low SPGI levels (<25 μg/l), whereas atrophic gastritis was found in only 2.2% of those men who had dyspeptic symptoms, but normal SPGI levels (≥50 μg/l). This is in agreement with earlier observations and suggests that SPGI is

Table III. Neoplastic lesions according to the presence (AG+) of moderate or severe atrophic gastritis in the corpus mucosa and the site of the tumour in the stomach in 63 men with neoplastic lesions

	Neoplastic lesion, *n* (% of total)				
Endoscopic finding	Total	Cancer	Dysplasia, high grade	Dysplasia, low grade	Carcinoid tumour
Total ($n = 1344$)	63 (100)	11	7	42	3
Unoperated stomach ($n = 1180$)	51 (100)	10	5	33	3
AG+ ($n = 1044$)	45 (88)	9	4	31	1
AG+ and lesion in angulus, corpus, fundus or cardia	29 (57)	8	4	16	1
AG+ and lesion in distal stomach	16 (31)	1	0	15	0
Operated stomach (earlier partial resection; $n = 164$)	12 (100)	1	2	9	0
AG+ ($n = 123$)	9 (75)	1	2	6	0

AG+ = the presence of advanced (moderate or severe) atrophic gastritis in corpus mucosa (endoscopic biopsies).

a good serological marker for identifying subjects with advanced atrophic corpus gastritis.

In a previous study of 3 population-based family samples from Finland (16), SPGI was <25 μg/l in 80% of subjects with severe atrophic corpus gastritis, but in only 2.1% of those without atrophic gastritis. In a recent investigation from the UK (17), SPGI levels <80 ng/ml and the presence of Helicobacter positivity disclosed corpus atrophy with a sensitivity and specificity of 89% and 92%, respectively. In that study, using the SPGI/SPGII ratio as an additional screening criterion (cut-off level 2.5) resulted in a slight increase in specificity, but a reduction of the sensitivity to 78%. In a Swedish study (18), the SPGI/SPGII ratio (cut-off level 5.5) was found to be the most sensitive test for corpus atrophy, the sensitivity and specificity being 99% and 94%, respectively. The prevalence of atrophic gastritis varied in these studies; thus, sensitivity and specificity figures are not fully comparable.

In our study, the prevalence of gastric neoplasia (cancer, dysplasia, carcinoid tumour) was 4.7% in those with low SPGI levels, whereas it was only 0.7% in those with normal SPGI levels. In men with unoperated stomachs, 13 of 15 (87%) with cancer or dysplasia of high grade had advanced (moderate or severe) atrophic gastritis in corpus biopsies and, furthermore, 12 (80%) had neoplastic lesions in the proximal part of the stomach, emphasizing the topographic association between the site of cancer and the site of atrophic gastritis in the stomach.

We identified seven men with gastric dysplasia of high grade. An endoscopic follow-up of these (19), in addition to similar earlier investigations (20–22), revealed that the development of an invasive cancer is an ultimate result in a few years in all patients with dysplasia of high grade. In Japan, these lesions are commonly diagnosed as intramucosal cancers (23). The rate of progression of dysplasia of low grade to malignant tumour, or to dysplasia of high grade is, on the other hand, much lower during a time period of some years, but progression may occur in 20% of patients (19). Thus, at least 18 cases with serious gastric tumours (11 cancers and 7 dysplasias of high grade) of life-threatening potential were identified in the present study among the 22,436 men screened for SPGI, and among the 1344 (6%) men subsequently endoscopied. This is a higher rate than the prevalence rate of cancer in ordinary endoscopy materials of dyspeptic out-patients in Finland (24, 25).

None of the 4 advanced gastric cancer patients survived 5 years, whereas 11 (78%) of 14 patients with early cancer or dysplasia of high grade survived 5 years (none of the deceased patients died, however, from gastric cancer). Correspondingly, only 33% of those gastric cancer patients of the ATBC study participants in whom the cancer was diagnosed by standard clinical practice survived 5 years. This prognostic improvement is obviously a consequence of the SPGI screening–endoscopy procedure, which cross-sectionally discovers gastric cancers or precursor lesions that are at early developmental stages. It is plausible that the present diagnostic procedure detected asymptomatic early cancers and late precancer lesions which would have appeared as symptomatic tumours during the subsequent 2–5 years.

Screening of asymptomatic populations with SPG methods has been performed earlier, particularly in Japan (26, 27). In these investigations, in addition to SPGI, the ratio of SPGI to SPGII has been used as a criterion for assessing atrophic gastritis and cancer risk. In Japan, these studies have generated good results comparable to, or better than, the results from mass screenings of gastric cancer with X-ray (28–30). They have presented results that indicate a cancer detection rate of even 1%–2% among those testing positive (29, 31), and that the cancers are discovered at earlier stages than with X-ray (27, 30). These observations are in agreement with our findings. In our study, the cancer detection rate was 0.8% among subjects with low SPGI levels. In addition, most of the neoplasms found were early cancers or definite precancer lesions. The detection rates of early cancers in Japan are reported to be 0.8%–1.0% of subjects testing positive. Our detection rate was 1.3% if the cases with dysplasia of high grade are considered to be intramucosal cancers, as is the case in Japan (23).

In Japan, the SPG methods are reported to disclose 50%–60% of all cancer cases (30–33), these percentages being even higher in age groups below 40 years (34). In an Italian study (35), 76%–96% of cancers tested positive when an index of SPGI and serum gastrin (gastrin × SPGI) was used. In the study of Nomura et al. (36), low SPGI levels were found in 15 (31%) of 48 cancer cases in a cohort of Japanese men in Hawaii. Low levels of gastrin-17 or SPGI were again found in 60% of patients with gastric cancer in a study from the UK (37). The present figures of low SPGI in gastric corpus atrophy patients among Finnish male smokers of 50–69 years of age with gastric cancer are much lower than those in any of the above studies. Only 26% of gastric cancer patients had SPGI levels <25 μg/l in a serum sample taken up to 3 years before the cancer diagnosis. These differences may mean that atrophic corpus gastritis (and low SPGI levels) varies in significance as a precancerous condition between populations and countries. Other varying factors may be methodologic. In Japanese studies, the cut-off level of SPGI is usually high (75 μg/l), which certainly results in higher cancer detection rates, but also into an increase in the endoscopy work load (26).

In our study population of 22,436 men, 85 had gastric cancer diagnosed within 5 years after the present SPGI testing and endoscopy, including the present 11 cancers. Assuming that the cases of high-grade dysplasia and early cancer would have developed into clinical gastric carcinomas in 5 years, this means that 14 cases (7 early gastric cancers and 7 high-grade dysplasias) were cured before advancing to a later stage and a poorer prognosis. Thus, in 5 years, the determination of SPGI with subsequent gastroscopy could reduce the number of cases with advanced, clinical cancer by approximately 15% (14 cases out of 92).

In the present study, the SPGI cut-off level (<25 μg/l) was arbitrary, and further studies are needed to optimize it. The study population consisted of only male smokers over 50 years of age and, therefore, additional studies are needed to clarify whether non-smoker males or females will benefit from the SPGI endoscopy procedure. Similarly, whether this practice results in lower gastric cancer mortality must be confirmed in studies designated to evaluate the benefits of the SPGI gastroscopy procedure. Our observations indicate, however, that only a proportion of gastric cancer cases can ever be detected with this procedure, since only one in four of all gastric cancer patients during a 3-year follow-up period had low SPGI levels at baseline.

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